a6 cont autonomous defect in EphB4 receptor-expressing venous cells, and an autonomous defect in the arteries themselves.

Amendments to the specification are indicated in the attached "Marked Up Version of Amendments" (pages i-iv).

In the Claims

Please cancel Claims 1-44 and 51-76. Claims 45-50 have been amended and are presented below in amended form and new Claims 77-150 have been added. In accordance with 37 C.F.R. § 1.121(c)(1)(ii), amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (page v-ix).

45. (Amended) A method for identifying an agent that inhibits interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, comprising:

(a) combining:

(1) the arterial cell-specific surface molecule;

(2) the venous cell-specific surface molecule; and

(3) the agent to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

a7 (b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the ~~molecule~~ of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is less in the presence of the agent than in the absence of the agent, the agent is one which inhibits interaction of the arterial cell-specific molecule of (1) with the venous cell-specific molecule of (2).

46. (Amended) A method for identifying an agent that inhibits interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the arterial cell-specific surface molecule is an Ephrin family ligand or a portion thereof and the venous cell-specific surface molecule is an Eph family receptor or a portion thereof, comprising:

(a) combining:

(1) the Ephrin family ligand or a portion thereof;

(2) the Eph family receptor or a portion thereof; and

(3) the agent to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is less in the presence of the agent than in the absence of the agent, the agent is one which inhibits interaction of the arterial cell-specific molecule of (1) with the vein cell-specific molecule of (2).

47. (Amended) A method for identifying an agent that inhibits interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the arterial cell-specific surface molecule is EphrinB2 or a portion thereof and the venous cell-specific molecule is EphB4 or a portion thereof, comprising:

(a) combining:

(1) EphrinB2 or a portion thereof;

(2) EphB4 or a portion thereof; and

(3) the agent to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is less in the presence of the agent than in the absence of the agent, the agent is one which inhibits interaction of the arterial cell-specific molecule of (1) with the vein cell-specific molecule of (2).

48. (Amended) A method for identifying an agent that enhances interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, comprising:

(a) combining:

(1) the arterial cell-specific surface molecule;

(2) the venous cell-specific surface molecule; and

(3) the agent to be assessed for its ability to enhance interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is greater in the presence of the agent than in the absence of the agent, the agent is one

which enhances interaction of the arterial cell-specific molecule of (1) with the venous cell-specific molecule of (2).

49. (Amended) A method for identifying an agent that enhances interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the arterial cell-specific surface molecule is an Ephrin family ligand or a portion thereof and the venous cell-specific surface molecule is an Eph family receptor or a portion thereof, comprising:

(a) combining:

(1) the Ephrin family ligand or a portion thereof;

(2) the Eph family receptor or a portion thereof; and

(3) the agent to be assessed for its ability to enhance interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is greater in the presence of the agent than in the absence of the agent, the agent is one which enhances interaction of the arterial cell-specific molecule of (1) with the vein cell-specific molecule of (2).

50. (Amended) A method for identifying an agent that enhances interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, wherein the Ephrin family ligand is EphrinB2 or a portion thereof and the Eph family receptor is EphB4 or a portion thereof, comprising:

(a) combining:

(1) EphrinB2 or a portion thereof;

(2) EphB4 or a portion thereof; and

(3) the agent to be assessed for its ability to enhance interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

(b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent of interaction determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the agent to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is greater in the presence of the agent than in the absence of the agent, the agent is one which enhances interaction of the arterial cell-specific molecule of (1) with the venous cell-specific molecule of (2).

77. (New) The method of Claim 45 wherein

(a) the arterial cell-specific surface molecule is selected from the group consisting of a protein, a soluble portion of a protein and a fusion protein;

(b) the venous cell-specific surface molecule is selected from the group consisting of a protein, a soluble portion of a protein and a fusion protein;

(c) both (a) and (b).

78. (New) The method of Claim 45 wherein

(a) the interaction between the arterial cell-specific molecule and the venous cell-specific molecule is determined by detecting binding of the arterial cell-specific molecule, wherein the arterial cell-specific molecule comprises a label; or

(b) the interaction between the arterial cell-specific molecule and the venous cell-specific molecule is determined by detecting binding of the venous cell-specific molecule, wherein the venous cell-specific molecule comprises a label.

79. (New) The method of Claim 78 wherein the label in (a) or the label in (b) is selected from the group consisting of a radioactive label, a fluorescent label and a colorimetric label.

80. (New) The method of Claim 45 wherein the agent is selected from the group consisting of a peptide, a polypeptide, a peptoid, a sugar, a hormone and a nucleic acid molecule.

81. (New) The method of Claim 45 wherein the agent is an organic compound.

82. (New) The method of Claim 45 wherein
(a) the arterial cell-specific surface molecule is expressed on a cell;
(b) the venous cell-specific surface molecule is expressed on a cell; or
(c) both (a) and (b).

83. (New) The method of Claim 45 wherein
(a) the arterial cell-specific surface molecule is expressed on an isolated arterial endothelial cell;
(b) the venous cell-specific surface molecule is expressed on an isolated venous endothelial cell; or
(c) both (a) and (b).

84. (New) The method of Claim 45 wherein
(a) the arterial cell-specific surface molecule is expressed on a cell derived from an isolated arterial endothelial cell;
(b) the venous cell-specific surface molecule is expressed on a cell derived from an isolated venous endothelial cell; or
(c) both (a) and (b).

85. (New) The method of Claim 45 wherein
(a) the arterial cell-specific surface molecule is expressed on a cell which has been genetically modified to express the arterial cell-specific surface molecule;

(b) the venous cell-specific surface molecule is expressed on a cell which has been genetically modified to express the venous cell-specific surface molecule; or

(c) both (a) and (b).

86. (New) The method of Claim 45 wherein

(a) the arterial cell-specific surface molecule is conjugated to a solid support and the venous cell-specific surface molecule is diffusible; or

(b) the venous cell-specific surface molecule is conjugated to a solid support and the arterial cell-specific surface molecule is diffusible.

87. (New) The method of Claim 86 wherein the solid support in (a) or (b) is selected from the group consisting of a bead, column pore glass, a pin and the wall of a plate.

88. (New) The method of Claim 46 wherein

(a) the interaction between the molecule of (1) and the molecule of (2) is determined by detecting binding of the molecule of (1), wherein the molecule of (1) comprises a label; or

(b) the interaction between the molecule of (1) and the molecule of (2) is determined by detecting binding of the molecule of (2), wherein the molecule of (2) comprises a label.

89. (New) The method of Claim 88 wherein the label in (a) or the label in (b) is selected from the group consisting of a radioactive label, a fluorescent label and a colorimetric label.

90. (New) The method of Claim 46 wherein the agent is selected from the group consisting of a peptide, a polypeptide, a peptoid, a sugar, a hormone and a nucleic acid molecule.

91. (New) The method of Claim 46 wherein the agent is an organic compound.

92. (New) The method of Claim 46 wherein
(a) the Ephrin family ligand or portion thereof is expressed on a cell;
(b) the Eph family receptor or portion thereof is expressed on a cell; or
(c) both (a) and (b).

93. (New) The method of Claim 46 wherein
(a) the Ephrin family ligand or portion thereof is expressed on an isolated arterial endothelial cell;
(b) the Eph family receptor or portion thereof is expressed on an isolated venous endothelial cell; or
(c) both (a) and (b).

94. (New) The method of Claim 46 wherein
(a) the Ephrin family ligand or portion thereof is expressed on a cell derived from an isolated arterial endothelial cell;
(b) the Eph family receptor or portion thereof is expressed on a cell derived from an isolated venous endothelial cell; or
(c) both (a) and (b).

95. (New) The method of Claim 46 wherein
(a) the Ephrin family ligand or portion thereof is expressed on a cell which has been genetically modified to express the Ephrin family ligand or portion thereof;
(b) the Eph family receptor or portion thereof is expressed on a cell which has been genetically modified to express the Eph family receptor or portion thereof; or
(c) both (a) and (b).

96. (New) The method of Claim 46 wherein
(a) the Ephrin family ligand or portion thereof is conjugated to a solid support and the Eph family receptor or portion thereof is diffusible; or
(b) the Eph family receptor or portion thereof is conjugated to a solid support and the Ephrin family ligand or portion thereof is diffusible.

97. (New) The method of Claim 96 wherein the solid support in (a) or (b) is selected from the group consisting of a bead, column pore glass, a pin and the wall of a plate.

98. (New) The method of Claim 46 wherein
(a) the Ephrin family ligand or portion thereof is a fusion protein;
(b) the Eph family receptor or portion thereof is a fusion protein; or
(c) both (a) and (b).

99. (New) The method of Claim 98 wherein
(1) the fusion protein in (a) comprises an Fc domain;
(2) the fusion protein in (b) comprises an Fc domain; or
(3) both (1) and (2).

100. (New) The method of Claim 98 wherein
(1) the fusion protein in (a) comprises an Fc domain of an IgG molecule;
(2) the fusion protein in (b) comprises an Fc domain of an IgG molecule; or
(3) the fusion protein in (a) and (b) comprises an Fc domain of an IgG molecule.

101. (New) The method of Claim 47 wherein
(a) the interaction between the molecule of (1) and the molecule of (2) is determined by detecting binding of the molecule of (1), wherein the molecule of (1) comprises a label; or
(b) the interaction between the molecule of (1) and the molecule of (2) is determined by detecting binding of the molecule of (2), wherein the molecule of (2) comprises a label.

102. (New) The method of Claim 101 wherein the label in (a) or the label in (b) is selected from the group consisting of a radioactive label, a fluorescent label and a colorimetric label.

103. (New) The method of Claim 47 wherein the agent is selected from the group consisting of a peptide, a polypeptide, a peptoid, a sugar, a hormone and a nucleic acid molecule.

104. (New) The method of Claim 47 wherein the agent is an organic compound.

105. (New) The method of Claim 47 wherein
(a) EphrinB2 or a portion thereof is expressed on a cell;
(b) EphB4 or a portion thereof is expressed on a cell; or
(c) both (a) and (b).

106. (New) The method of Claim 47 wherein
(a) EphrinB2 or a portion thereof is expressed on an isolated arterial endothelial cell;
(b) EphB4 or a portion thereof is expressed on an isolated venous endothelial cell; or
(c) both (a) and (b).

107. (New) The method of Claim 47 wherein
(a) EphrinB2 or a portion thereof is expressed on a cell derived from an isolated arterial endothelial cell;
(b) EphB4 or a portion thereof is expressed on a cell derived from an isolated venous endothelial cell; or
(c) both (a) and (b).

108. (New) The method of Claim 47 wherein
(a) EphrinB2 or a portion thereof is expressed on a cell which has been genetically modified to express EphrinB2 or a portion thereof;
(b) EphB4 or a portion thereof is expressed on a cell which has been genetically modified to express EphB4 or a portion thereof; or
(c) both (a) and (b).

109. (New) The method of Claim 47 wherein
   (a) EphrinB2 or a portion thereof is conjugated to a solid support and EphB4 or a portion thereof is diffusible; or
   (b) EphB4 or a portion thereof is conjugated to a solid support and EphrinB2 or a portion thereof is diffusible.

110. (New) The method of Claim 109 wherein the solid support in (a) or (b) is selected from the group consisting of a bead, column pore glass, a pin and the wall of a plate.

111. (New) The method of Claim 47 wherein
   (a) EphrinB2 or a portion thereof is a fusion protein;
   (b) EphB4 or a portion thereof is a fusion protein; or
   (c) both (a) and (b).

112. (New) The method of Claim 111 wherein
   (1) the fusion protein in (a) comprises an Fc domain;
   (2) the fusion protein in (b) comprises an Fc domain; or
   (3) both (1) and (2).

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113. (New) The method of Claim 111 wherein
   (1) the fusion protein in (a) comprises an Fc domain of an IgG molecule;
   (2) the fusion protein in (b) comprises an Fc domain of an IgG molecule; or
   (3) the fusion protein in (a) and (b) comprises an Fc domain of an IgG molecule.

114. (New) The method of Claim 48 wherein
   (a) the arterial cell-specific surface molecule is selected from the group consisting of a protein, a soluble portion of a protein and a fusion protein;
   (b) the venous cell-specific surface molecule is selected from the group consisting of a protein, a soluble portion of a protein and a fusion protein;
   (c) both (a) and (b).

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115. (New) The method of Claim 48 wherein
   (a) the interaction between the arterial cell-specific molecule and the venous cell-specific molecule is determined by detecting binding of the arterial cell-specific molecule, wherein the arterial cell-specific molecule comprises a label; or
   (b) the interaction between the arterial cell-specific molecule and the venous cell-specific molecule is determined by detecting binding of the venous cell-specific molecule, wherein the venous cell-specific molecule comprises a label.

116. (New) The method of Claim 115 wherein the label in (a) or the label in (b) is selected from the group consisting of a radioactive label, a fluorescent label and a colorimetric label.

117. (New) The method of Claim 48 wherein the agent is selected from the group consisting of a peptide, a polypeptide, a peptoid, a sugar, a hormone and a nucleic acid molecule.

118. (New) The method of Claim 48 wherein the agent is an organic compound.

119. (New) The method of Claim 48 wherein
   (a) the arterial cell-specific surface molecule is expressed on a cell;
   (b) the venous cell-specific surface molecule is expressed on a cell; or
   (c) both (a) and (b).

120. (New) The method of Claim 48 wherein
   (a) the arterial cell-specific surface molecule is expressed on an isolated arterial endothelial cell;
   (b) the venous cell-specific surface molecule is expressed on an isolated venous endothelial cell; or
   (c) both (a) and (b).

121. (New) The method of Claim 48 wherein
   (a) the arterial cell-specific surface molecule is expressed on a cell derived from an isolated arterial endothelial cell;
   (b) the venous cell-specific surface molecule is expressed on a cell derived from an isolated venous endothelial cell; or
   (c) both (a) and (b).

122. (New) The method of Claim 48 wherein
   (a) the arterial cell-specific surface molecule is expressed on a cell which has been genetically modified to express the arterial cell-specific surface molecule;
   (b) the venous cell-specific surface molecule is expressed on a cell which has been genetically modified to express the venous cell-specific surface molecule; or
   (c) both (a) and (b).

123. (New) The method of Claim 48 wherein
   (a) the arterial cell-specific surface molecule is conjugated to a solid support and the venous cell-specific surface molecule is diffusible; or
   (b) the venous cell-specific surface molecule is conjugated to a solid support and the arterial cell-specific surface molecule is diffusible.

a8 cont

124. (New) The method of Claim 123 wherein the solid support in (a) or (b) is selected from the group consisting of a bead, column pore glass, a pin and the wall of a plate.

125. (New) The method of Claim 49 wherein
   (a) the interaction between the molecule of (1) and the molecule of (2) is determined by detecting binding of the molecule of (1), wherein the molecule of (1) comprises a label; or
   (b) the interaction between the molecule of (1) and the molecule of (2) is determined by detecting binding of the molecule of (2), wherein the molecule of (2) comprises a label.

126. (New) The method of Claim 125 wherein the label in (a) or the label in (b) is selected from the group consisting of a radioactive label, a fluorescent label and a colorimetric label.

127. (New) The method of Claim 49 wherein the agent is selected from the group consisting of a peptide, a polypeptide, a peptoid, a sugar, a hormone and a nucleic acid molecule.

128 (New) The method of Claim 49 wherein the agent is an organic compound.

129 (New) The method of Claim 49 wherein

(a) the Ephrin family ligand or portion thereof is expressed on a cell;

(b) the Eph family receptor or portion thereof is expressed on a cell; or

(c) both (a) and (b).

130 (New) The method of Claim 49 wherein

(a) the Ephrin family ligand or portion thereof is expressed on an isolated arterial endothelial cell;

(b) the Eph family receptor or portion thereof is expressed on an isolated venous endothelial cell; or

(c) both (a) and (b).

131 (New) The method of Claim 49 wherein

(a) the Ephrin family ligand or portion thereof is expressed on a cell derived from an isolated arterial endothelial cell;

(b) the Eph family receptor or portion thereof is expressed on a cell derived from an isolated venous endothelial cell; or

(c) both (a) and (b).

132 (New) The method of Claim 49 wherein

(a) the Ephrin family ligand or portion thereof is expressed on a cell which has been genetically modified to express the Ephrin family ligand or portion thereof;

(b) the Eph family receptor or portion thereof is expressed on a cell which has been genetically modified to express the Eph family receptor or portion thereof; or

(c) both (a) and (b).

133 (New) The method of Claim 49 wherein

(a) the Ephrin family ligand or portion thereof is conjugated to a solid support and the Eph family receptor or portion thereof is diffusible; or

(b) the Eph family receptor or portion thereof is conjugated to a solid support and the Ephrin family ligand or portion thereof is diffusible.

134 (New) The method of Claim 133 wherein the solid support in (a) or (b) is selected from the group consisting of a bead, column pore glass, a pin and the wall of a plate.

135. (New) The method of Claim 49 wherein

(a) the Ephrin family ligand or portion thereof is a fusion protein;

(b) the Eph family receptor or portion thereof is a fusion protein; or

(c) both (a) and (b).

136. (New) The method of Claim 135 wherein

(1) the fusion protein in (a) comprises an Fc domain;

(2) the fusion protein in (b) comprises an Fc domain; or

(3) both (1) and (2).

137. (New) The method of Claim 135 wherein

(1) the fusion protein in (a) comprises an Fc domain of an IgG molecule;

(2) the fusion protein in (b) comprises an Fc domain of an IgG molecule; or

(3) the fusion protein in (a) and (b) comprises an Fc domain of an IgG molecule.

138. (New) The method of Claim 50 wherein
   (a) the interaction between the molecule of (1) and the molecule of (2) is determined by detecting binding of the molecule of (1), wherein the molecule of (1) comprises a label; or
   (b) the interaction between the molecule of (1) and the molecule of (2) is determined by detecting binding of the molecule of (2), wherein the molecule of (2) comprises a label.

139. (New) The method of Claim 138 wherein the label in (a) or the label in (b) is selected from the group consisting of a radioactive label, a fluorescent label and a colorimetric label.

140. (New) The method of Claim 50 wherein the agent is selected from the group consisting of a peptide, a polypeptide, a peptoid, a sugar, a hormone and a nucleic acid molecule.

141. (New) The method of Claim 50 wherein the agent is an organic compound.

142. (New) The method of Claim 50 wherein
   (a) EphrinB2 or a portion thereof is expressed on a cell;
   (b) EphB4 or a portion thereof is expressed on a cell; or
   (c) both (a) and (b).

143. (New) The method of Claim 50 wherein
   (a) EphrinB2 or a portion thereof is expressed on an isolated arterial endothelial cell;
   (b) EphB4 or a portion thereof is expressed on an isolated venous endothelial cell; or
   (c) both (a) and (b).

144. (New) The method of Claim 50 wherein
   (a) EphrinB2 or a portion thereof is expressed on a cell derived from an isolated arterial endothelial cell;
   (b) EphB4 or a portion thereof is expressed on a cell derived from an isolated venous endothelial cell; or
   (c) both (a) and (b).

145. (New) The method of Claim 50 wherein
   (a) EphrinB2 or a portion thereof is expressed on a cell which has been genetically modified to express EphrinB2 or a portion thereof;
   (b) EphB4 or a portion thereof is expressed on a cell which has been genetically modified to express EphB4 or a portion thereof; or
   (c) both (a) and (b).

146. (New) The method of Claim 50 wherein
   (a) EphrinB2 or a portion thereof is conjugated to a solid support and EphB4 or a portion thereof is diffusible; or
   (b) EphB4 or a portion thereof is conjugated to a solid support and EphrinB2 or a portion thereof is diffusible.

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147. (New) The method of Claim 146 wherein the solid support in (a) or (b) is selected from the group consisting of a bead, column pore glass, a pin and the wall of a plate.

148. (New) The method of Claim 50 wherein
   (a) EphrinB2 or a portion thereof is a fusion protein;
   (b) EphB4 or a portion thereof is a fusion protein; or
   (c) both (a) and (b).